Office Action Summary	Application No.	Applicant(s)	
	10/563,683	GLADWIN ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2010*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-3,5-15,17 and 18* is/are pending in the application.

5a) Of the above claim(s) *5-12* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3,13-15,17 and 18* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets, 12/22/2010; 1 sheet, 3/23/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's payment and submission filed 12/22/2010, has been received and entered into the present application. Accordingly, prosecution has been reopened.

Applicant's amendment filed 12/22/2010 has been received and entered into the present application.

As reflected by the attached, completed copy form PTO/SB/08A (three pages total), the Examiner has considered the cited references.

The declaration under 1.132 of Mark T. Gladwin filed 12/22/2010 has been received and is addressed herein.

Applicant's arguments, filed 12/22/2010 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections being applied to the instant application.

As was discussed in the interview which took place on November 14, 2011, it appears Applicant failed to address the obviousness rejections as a whole. Specifically, the arguments presented appear to be solely drawn to the teachings of Modin et al. Applicant is reminded that rejections made under 35 U.S.C. 103(a) are based upon the combination of references. As a result, focusing solely on the discrete teachings of one of the cited references is tantamount to examining each of them inside of a vacuum and fails to be persuasive in establishing non-obviousness because it is the *combined* teachings that are the basis for a proper conclusion of obviousness, not each individual reference alone. In other words, it must

be remembered that the references are relied upon in combination and are not meant to be considered separately.

Status of claims

Claim 1-3, 5-15 and 17-18 are pending.

Claims 5-12 remain withdrawn.

Claims 1-3, 13-15 and 17-18 are currently under examination and the subject matter of the present Office Action.

Priority

This application claims benefit of provisional application 60/485,959 filed 7/9/2003 and 60/511,244 filed 10/14/2003.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, 60/485,959 filed 7/9/2003 as well as 60/511,244 filed 10/14/2003., fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. All claims are not adequately supported or enabled by the prior-filed applications for a method for treating or ameliorating a condition selected from hepatic or cardiac or brain ischemia-reperfusion injury; pulmonary hypertension or cerebral artery vasospasm in a subject by decreasing blood pressure and/or increasing vasodilation in the subject, the method comprising administering *non-acidified* sodium nitrite to the subject to decrease the blood

pressure and/or increase vasodilation in the subject, thereby treating or ameliorating the condition. Specifically, the provisional applications fail to teach non-acidified sodium nitrite as instantly claimed. Thus, Applicant is not entitled to the priority date in these applications for *all* claims in the instant claim set because the information contained within the previous referred filings does not support the granting of an earlier filing date. The priority date granted is that of July 9, 2004 which is the filing date of the PCT application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 13-15 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (British Journal of Pharmacology, April 2003; of record) in view of Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition, 2002, page 1511) and Remington's Pharmaceutical Science (page 420-425, 1980) and Modin et al. (Acta Physiol Scand 2001).

Webb et al. teach a method of treating cardiac ischemia-reperfusion (I/R) injury with

administration via infusion of 10-1000 uM of inorganic nitrite. It was concluded that the production of nitric oxide protected against I/R injury as such may have an important therapeutic role in myocardial infarction. It should be noted that inorganic sodium nitrite, as stated in the Office Action mailed on 12/28/2009 on page 6, line 1, is interpreted to meet the claim.

Webb et al. is silent on the use of the salt, sodium nitrite and the administration of sodium nitrite in vivo via intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intraarterial, subcutaneous, inhalation and into cardiopulmonary bypass circuit.

Goldfrank et al. teach that administration of nitrite, such as sodium nitrite, induces vasodilation and enhances organ blood flow via denitration with subsequent release of nitric oxide (page 1511, left column). Further, the intravenous injection of sodium nitrite results is taught (page 1511, right column).

Remington's Pharmaceutical Sciences teaches that drugs may be formulated into salts to modify the duration of a drug, to modify the transportation and distribution of the drug in the body, to reduce toxicity and to overcome difficulties in pharmaceutical formulation procedures or in the dosage form itself (see column 2, page 424, first paragraph).

Modin et al. teach that nitric oxide is derived from nitrite (title) and that physiologically relevant concentrations of nitrite evoke vasodilation (page 13, right column Discussion; and page 15, left column last paragraph). Modin et al. teach that the relaxatory effect of nitrite was increased at pH 6.6 over neutral pH (Abstract). Thus Modin et al. teach that **non-acidified nitrite** also has relaxatory effects similar to "acidified" nitrite (see figures 1, 2, figure 5 and respective discussion in the text). Modin et al. administered various amounts of **sodium nitrite** but noted a threshold response of **10 microM** and near relaxation to basal tone at 1000 microM for the non-acidified sodium nitrite (page 11, Results). Modin et al. teach adding additional agents (ascorbic acid) to enhance the effect of the sodium nitrite (Abstract) Modin et al. conclude that inorganic nitrite evokes vasodilation most likely through nitric oxide release

and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during ischemia/hypoxia (page 15, last paragraph).

One of ordinary skill in the art would have been motivated to use intravenous as the route of administration because this route of administration is known to effective in administering sodium nitrite. Goldfrank et al. teach intravenous administration which provides the vasodilator to the systemic circulation. Additional forms of administration such as intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intraarterial, subcutaneous, inhalation and into a cardiopulmonary bypass circuit are obvious to one of ordinary skill in the art of medicine.

It would have been prima facie obvious to the skilled artisan by any one or more of these factors to formulate nitrite into a pharmaceutical acceptable salt, such as sodium nitrite, to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity in order to facilitate administration in vivo. Further, when administered in vivo via infusion, the sodium nitrite would contact the blood. Finally, one of ordinary skill in the art would have had a reasonable expectation that the therapeutic benefit of the agent in salt form would have the same or substantially similar to that of the agent itself.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use sodium nitrite within the range instantly claimed. One of ordinary skill in the art would have been motivated to do this because Shaw et al. teach *a therapeutically effective amount* to the systemic circulation to treat an ischemic condition in a patient and Modin et al. suggest how much sodium nitrite would be beneficial for use in tissues during ischemia. Modin et al. also indicate that human plasma has 0.45 microM nitrite and human serum has 6.6 microM nitrite (page 14, left column) so it is obvious to administer an amount of nitrite that would increase the plasma and serum concentration above the basal level for a therapeutic effect. It is merely routine optimization to obtain a circulating concentration.

It is well within the skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen and/or schedule of administration that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed.

Further with regard to the concentrations cited, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 1-3, 13-15 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (US 4,650,484) in view of Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition, 2002, page 1511) and Modin et al. (Acta Physiol Scand 2001).

Shaw et al. disclose methods for treating **ischemic conditions** in a patient having such a condition by administration of a therapeutically effective amount of a vasodilator internally and transdermally to treat the condition (Abstract and claims 1-13). Shaw et al. teach **buccal** administration to get the

vasodilator into the systemic circulation which means that it contacts the blood (claim 7). The nitrite, therefore, reacts in the presence of hemoglobin in the subject to release nitric oxide. **Sodium nitrite**, which is not acidified, is specifically named as a vasodilator in a finite list of vasodilators (column 2, lines 35-45). The method is to increase the supply of oxygen to the tissue such as the heart, which would be an ischemic heart (ischemic cardiac tissue and hence a cardiovascular condition) (column 2, lines 51-68). The vasodilator is administered with another agent, which is another vasodilator (claim 1).

Shaw et al. is silent on the route of administration selected from the group consisting of intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intra-arterial, subcutaneous, inhalation and into a cardiopulmonary bypass circuit.

Goldfrank et al. teach that administration of nitrite, such as sodium nitrite, induces vasodilation and enhances organ blood flow via denitration with subsequent release of nitric oxide (page 1511, left column). Further, the intravenous injection of sodium nitrite results is taught (page 1511, right column).

Modin et al. teach that nitric oxide is derived from nitrite (title) and that physiologically relevant concentrations of nitrite evoke vasodilation (page 13, right column Discussion; and page 15, left column last paragraph). Modin et al. teach that the relaxatory effect of nitrite was increased at pH 6.6 over neutral pH (Abstract). Thus Modin et al. teach that **non-acidified nitrite** also has relaxatory effects similar to "acidified" nitrite (see figures 1, 2, figure 5 and respective discussion in the text). Modin et al. administered various amounts of **sodium nitrite** but noted a threshold response of **10 microM** and near relaxation to basal tone at 1000 microM for the non-acidified sodium nitrite (page 11, Results). Modin et al. teach adding additional agents (ascorbic acid) to enhance the effect of the sodium nitrite (Abstract) Modin et al. conclude that inorganic nitrite evokes vasodilation most likely through nitric oxide release and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during **ischemia**/hypoxia (page 15, last paragraph).

One of ordinary skill in the art would have been motivated to use injection as the route of administration because Shaw et al. is directed to getting the vasodilator into the systemic circulation. Goldfrank et al. teach intravenous administration which provides the vasodilator to the systemic circulation. Additional forms of administration such as intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intraarterial, subcutaneous, inhalation and into a cardiopulmonary bypass circuit are obvious to one of ordinary skill in the art of medicine especially when Shaw et al. is directed to getting the vasodilator into the systemic circulation.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use sodium nitrite within the range instantly claimed. One of ordinary skill in the art would have been motivated to do this because Shaw et al. teach *a therapeutically effective amount* to the systemic circulation to treat an ischemic condition in a patient and Modin et al. suggest how much sodium nitrite would be beneficial for use in tissues during ischemia. Modin et al. also indicate that human plasma has 0.45 microM nitrite and human serum has 6.6 microM nitrite (page 14, left column) so it is obvious to administer an amount of nitrite that would increase the plasma and serum concentration above the basal level for a therapeutic effect. It is merely routine optimization to obtain a circulating concentration.

Further with regard to the concentrations cited, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

It is obvious from the above teachings that Shaw et al. expressly contemplates variation in the dosage amounts and specifically acknowledges that such a matter was well within the skill of the artisan

at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen and/or schedule of administration that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed.

Response to Applicant's Remarks

Applicant alleges that none of the cited references teach or even suggest that non-acidified nitrite is a vasodilator in vivo. This is not found persuasive. Webb et al. teach a method of treating cardiac ischemia-reperfusion (I/R) injury with administration via infusion of 10-1000 uM of inorganic nitrite. It was concluded that the production of nitric oxide protected against I/R injury as such may have an important therapeutic role in myocardial infarction. It should be noted that inorganic sodium nitrite, as stated in the Office Action mailed on 12/28/2009 on page 6, line 1, is interpreted to meet the claim. Further, Shaw et al. disclose methods for treating ischemic conditions in a patient having such a condition by administration of a therapeutically effective amount of a vasodilator internally and transdermally to treat the condition (Abstract and claims 1-13). The nitrite, therefore, reacts in the presence of hemoglobin in the subject to release nitric oxide. Sodium nitrite, which is not acidified, is specifically named as a vasodilator in a finite list of vasodilators.

Applicant alleges that Lauer et al. teaches that "nitrite lacks intrinsic vasodilator action." This is not found persuasive. Applicant is drawn to the breadth of claim 1 which recites "administering a therapeutically effective amount of non-acidified sodium nitrite..." In the instant case of Lauer et al., it

seems that the investigators simply measured endogenous NO concentrations, rather than actually administering non-acidified sodium nitrite as is recited in the claim.

Applicant alleges that Modin et al. would not have any motivation to optimize non-acidified nitrite because it teaches that acidified nitrite is a "significantly better vasodilator." This is not found persuasive. Modin et al. teaches that "nitrites have long been known to act as vasodilating substances" and states that "the aim of the present study was to investigate whether nitrite in a physiologically relevant concentration... would act as a vasodilator" (column 1, page 10). Modin concludes that "the importance of the present results is that when both nitrite concentration and pH values are kept within the normal physiological range, vasodilation occurs with parallel release of NO." Therefore Modin teaches that nitrite in physiological conditions acts as a vasodilator.

Applicant alleges that Modin et al. employ an in vitro system which is not representative of an in vivo effect. Applicant repeatedly alleges that the experiments in Modin et al. are performed in isolated aortic rings without blood in them and therefore employ an in vitro system which is not representative of an in vivo effect. "Because these studies required non-physiological conditions – extremely low oxygen tension and low pH, as well as high nitrite concentrations – they were not considered by those in the art to reflect what would happen in the human circulation." Applicant cites paragraph 4 of the Kelm declaration, paragraph 5 of the Ignarro Declaration and paragraph 3 of the Lundberg Declaration which were previously submitted. Applicant has further submitted the declaration under 37 C.F.R. 1.132 by Mark T. Gladwin. Declarant alleges that the lack of red blood cells and hemoglobin in the aortic ring bioassay do not render the results representative in vivo. Declarant alleges that all three of the cited references "do not provide any comparison between any in vitro aortic ring assay an in vivo system for the particular studies being described."

Applicant's contention remains that the teachings of Modin are not predictive in an *in vivo* setting. Declarant alleges that "none of the references cited in the July 27, 2010 Office Action teach that vasodilatory concentrations of nitrite or NO in vivo correlate with vasodilatory concentrations in an aortic ring bioassay." Declarant has failed to state how they have come to this conclusion. As was extensively discussed in the Final Rejection of 7/27/2010, the state of the art at the time of the invention reveals that the aortic ring bioassay is predictive *in vivo*. This was evidenced by several references which were previously presented and reiterated below:

(i) U.S. 6,153,186 teaches the use of aortic ring bioassays and that this data is fully commensurate with the in vivo findings (column 7, lines 64-65);

(ii) U.S. 5,436,271 teaches the use of rat aortic rings to test the effect of N-(hydrazinoiminomethyl)-L-lysine and further teaches of the compound for treatment in a subject (column 9, lines 42-45 and claim 1);

(iii) U.S. 6,110,453 teaches that Fig. 3 illustrates the time course of vascular relaxation when different doses of the poly-bound nitric oxide-releasing composition is exposed to the aortic ring, causes relaxation, then withdrawn from the organ bath, allowing restriction to occur, then reintroduced into the organ bath, causing the vessel to dilate again. It is concluded that the experiment illustrates the pharmacological effects of the polymer-bound nitric oxide/nucleophile composition which is particularly advantageous to localize the effects of nitric oxide release to a specific target organ (column 3, last full paragraph and column 4, lines 1-3).

(iv) Gladwin et al. (Free Radical Biology & Medicine, available online 1/4/2004). The primary inventor of the instant application states in the instant article (page 710, column bridging column 2 to page 711, column 1, first paragraph):

> "mechanisms proposed for the in vivo conversion of nitrite to NO include enzymatic reduction by xanthine oxidoreductase and nonenzymatic disproportionation/acidic reduction.... Indeed, *consistent* with oxygen- and pH- sensitive chemistry, hypoxia and acidosis potentiate NO generation and vasodilation from both nitrite and NO donors in *aortic ring bioassay* and lung perfusion bioassay systems (emphasis added)."

Though, the remarks of the Applicant had Declarant has been noted, the art including the primary inventor clearly teach that results found from the aortic ring bioassay are also found in an *in vivo* environment. Therefore, it is reasonable predictive that the results found *in vitro* can be extrapolated to an *in vivo* environment. Applicant appears to be applying a standard of absolute predictability in order to find obviousness which is not required. Rather, to find obviousness, only a reasonable expectation of success is required, which is provided supra. Please see MPEP 2143.02. Additionally, Applicant is guided to MPEP 2121[R-6](I), which states, "When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable." Declarant has guided the Examiner to the teachings of Fujiwara et al. which allegedly "illustrates that as little as 1 uM hemoglobin inhibits NO-induced vasodilation in a ring bioassay." This is not found persuasive. Fig 5A of Fujiwara which Declarant specifically guides the Examiner to actually measures acetylcholine induced vasodilation, in contrast to the claimed non-acidified sodium nitrite:

FIG. 5. Typical patterns of blockade of the acetylcholine (ACh)-induced vasodilation of rabbit basilar artery previously contracted by 10^{-6} M serotonin (5-HT). A: Hemoglobin,

Declarant alleges that the cited U.S. '186 nor the cited U.S. '271 or Declarants own publication (Free Radical Biology & Medicine, available online 1/4/2004), present experiments which "measure the vasodilatory activity of nitrite." This is not found persuasive. Again it is reminded that the references were cited in order to present the state of the art at the time of the filing of this instant application. U.S. '186 was cited for its teachings that the aortic ring bioassays data is commensurate with the results found in an *in vivo* setting. Declarant alleges that cited U.S. '453 describes an NI-release molecule which "is not

at all the same as the anion nitrite." Declarant further states that "NO donors are known to be inhibited by hemoglobin." Declarant has previously alleged that hemoglobin inhibits NO-induced vasodilation, and therefore concludes that since an *in vitro* setting does not account for hemoglobin, the in vitro setting is not predictive. However, the teachings of U.S. '453, "concluded that the experiment illustrates the pharmacological effects of the polymer-bound nitric oxide/nucleophile composition which is particularly advantageous to localize the effects of nitric oxide release to a specific target organ." Therefore, the teachings of U.S. '453 account for hemoglobin in that the *in vitro* results have been confirmed *in vivo*.

Arguendo the above, it is noted that the limitation "wherein the sodium nitrite is administered to a circulating concentration of about 0.6 to 240 uM...." is not a dosage which is actually given at the time of administration, as was confirmed by Applicant on the interview which took place November 14, 2011. Rather, it is a concentration of the agent which is present in the body after administration. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided

the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 13-15 and 17-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 10 and 14-18 of copending Application No. 12/748,184. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the instant invention embraces or is embraced by the subject matter of the copending application. One of ordinary skill in the art would recognize the methods in the copending application of treating hepatic or cardiac or brain ischemia-reperfusion injury by decreasing blood pressure or increasing vasodilation with a non-acidified sodium nitrite to a subject as embracing the subject matter of instant claims 1-3, 13-15 and 17-18. The same concentrations of sodium nitrite are claimed as well as the subjects and routes of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

CONCLUSION

No claim is found to be allowable.

All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 7am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP
/Brandon J Fetterolf/
Supervisory Patent Examiner, Art Unit 1628